A convenient method of preparing optically active (*S*)-*N*-tritylaziridine-2-carboxylate esters from (*S*)-β-haloamino acids

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A convenient method of preparing optically active (*S*)-*N*-tritylaziridine-2-carboxylate esters *via* intramolecular cyclization of (*S*)-*N*-trityl-β-haloamino acid esters is described.

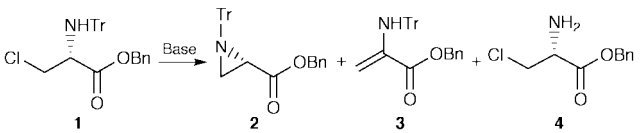
The development of novel methods of synthesizing optically pure unnatural amino acids is an area of current interest.[1] (*S*)-*N*-Tritylaziridine-2-carboxylate [*N*-Tr-(*S*)-AZC] esters represent an interesting class of compounds since they can be considered a versatile synthetic equivalent of the 'β-alanyl cation' synthon suitable for elaboration into β-substituted (*S*)-amino acids,[2] enzyme substrates,[3] and irreversible inhibitors of proteases.[4] Despite their importance for synthetic use, only a few studies on the syntheses of *N*-Tr-(*S*)-AZC esters have been reported [5–9] and these methods involve multi-step procedures, require expensive starting materials, and produce a low yield or partial racemization of the intermediate in the synthetic scheme.

During the course of our studies on the application of enzymes in organic syntheses, we have discovered an efficient method for the production of halogen-containing α-amino acids *via* chemo-enzymatic reaction.[10] Using this process, optically pure (*S*)-β-haloamino acids, especially, (*S*)-β-chloroalanine (BCA) and *threo*-(2*R*,3*S*)-3-chloroaspartic acid, can be obtained in large quantities. We report herein a convenient method of synthesizing *N*-Tr-(*S*)-AZC esters *via* intramolecular cyclization of (*S*)-*N*-trityl-β-chloroalanine (*N*-Tr-BCA) esters,† which were derived from the enzymatically prepared BCA (Scheme 1).

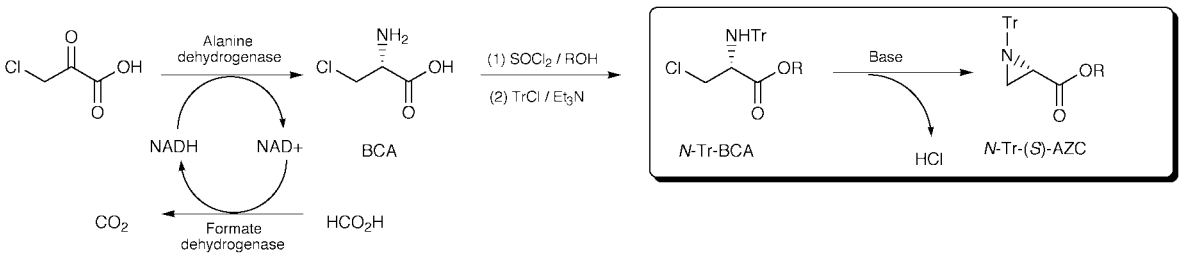
In our first attempt at a base-catalyzed intramolecular cyclization reaction of *N*-Tr-BCA benzyl ester **1** to benzyl *N*-Tr-(*S*)-AZC **2** with 2 equiv. of strong base, such as NaH, Bu^{t}OK, DBU, DBN and Bu^{t}Li, in THF at room temperature, however, only the 1,2-elimination of hydrogen and chloride atoms occurred and *N*-trityldehydroalanine benzyl ester **3**‡ was obtained as the sole product (Table 1, entry 1). Reaction in another solvent, such as hexane, Et_2O, CH_2Cl_2, MeCN, DMF and DMSO, also gave **3**. It turned out that the expected aziridine **2**§ was formed when a weak inorganic base, KF, was used as the base in refluxing MeCN (entry 2) with some formation of **3**. Encouraged by this result, we further investigated the inorganic bases by changing their basicity and counter ions. Weaker bases and neutral salts such as LiF, NaF, LiCl, NaCl, KCl, NaBr, KBr, CsBr, RbBr, MgF_2 and SrF_2 were ineffective and afforded BCA benzyl ester **4** which was formed by deprotection of the trityl group of **1** (entry 4). However, the use of bisulfite salt, $KHSO_3$, could suppress both the 1,2-elimination and deprotection reaction to give the aziridine **2** as the sole product, although the reaction rate was decreased to one-third of that with KF (entry 5). Elongation of the reaction time could solve this problem and afforded **2** in almost quantitative yield (entry 6). The choice of the reaction solvent was quite important; alkyl nitriles *i.e.* MeCN, EtCN, PrCN, Pr^{i}CN, BuCN and Bu^{i}CN, were the only suitable solvents to form aziridine **2**. Other organic solvents such as THF, DMSO, DMF, 1,4-dioxane, CH_2Cl_2 and Et_2O were not useful; only the recovery of the starting material **1** was observed. The other weak acid salts of the potassium ion, $KHSO_3$, K_2SO_3, K_2HPO_4, K_2WO_4 and $K_2S_2O_5$, and weak organic amines, Et_3N and Pr^i_2NEt, were effective bases for the cyclization reaction and gave the cyclized aziridine **2** as the sole product. Interestingly, only a deprotected compound **4** was obtained using sulfate and persulfate salts, $KHSO_4$, K_2SO_4 and $K_2S_2O_7$. However, the use of stronger inorganic bases such as RbF and CsF deserves comment and produced only **3** (*e.g.* entry 7).

Under such suitable conditions,¶ the cyclization reactions of various esters of *N*-Tr-BCA were examined. Methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, isopropyl and isobutyl esters of BCA were converted to the corresponding aziridines in yields of 90, 95, 94, 98, 92, 97 and 96%, respectively. These results suggest

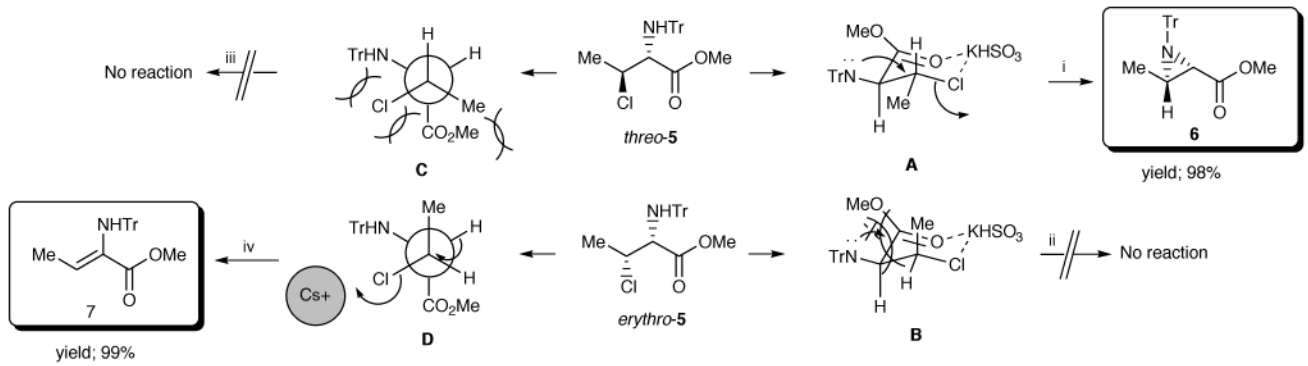
Table 1 Base-catalyzed transformation of (*S*)-*N*-Tri-β-chloroalanine benzyl ester



				Products (%)			
Entry	Base	Solvent	Conditions	**1**	**2**	**3**	**4**
1	NaH	THF	rt 4 h	0	0	95	0
2	KF	MeCN	reflux, 24 h	0	64	36	0
3	KF	DMF	90 °C, 4 h	0	0	98	0
4	NaF	MeCN	reflux, 24 h	0	5	2	90
5	$KHSO_3$	MeCN	reflux, 24 h	66	34	0	0
6	$KHSO_3$	MeCN	reflux, 48 h	0	98	0	0
7	CsF	MeCN	reflux, 4 h	0	0	97	0



Scheme 1 Chemoenzymatic synthesis of (*S*)-*N*-tritylaziridine-2-carboxylate esters.



Scheme 2 *Reagents and conditions*: i, $KHSO_3$, MeCN, reflux, 63 h; ii, $KHSO_3$, MeCN, reflux, 120 h; iii, CsF, DMF, 100 °C, 60 h; iv, CsF, MeCN, reflux, 4 h.

that changing the ester moiety does not affect the yield or reaction rate of the formation of aziridine.

Based on these observations, we propose the following reaction mechanisms for the cyclization or 1,2-elimination reactions: (i) when the reagent is neutral or has Lewis acidity, only deprotection of the trityl group is seen; (ii) if the reagent exhibits basicity and dissociates into ions, the metal ions act as a base and catalyzed the 1,2-elimination reaction; (iii) if the reagent cannot dissociate into ions, it chelates both the chloride atom and carbonyl oxygen, allowing the cyclization reaction. This is supported by the fact that the KF-catalyzed cyclization reaction proceeds only in MeCN; the 1,2-elimination reaction preferentially occurred in polar solvents, such as DMF, DMSO, THF and 1,4-dioxane, in which the reagents dissociate more easily into the ion pairs (*e.g.* Table 1, entry 3).

We next examined the cyclization or 1,2-elimination reaction for each diastereomer of methyl (*S*)-*N*-trityl-3-chloro-2-amino-butyrate (*N*-Tr-BCAB), prepared from (*S*)-threonine or *allo*-(*S*)-threonine. As shown in Scheme 2, only the *threo* isomer of *N*-Tr-BCAB (*threo*-**5**) was cyclized to form (2*S*,3*R*)-3-methylaziridine-2-carboxylate **6**,‖ but *erythro*-**5** was not. If we assume a chair-like transition state, we can conceive a reaction mechanism. In the transition state, $KHSO_3$, which does not dissociate into K^+ and HSO_3^-, is chelated by both the chloride atom and the carbonyl oxygen; it allows an attack by a lone pair from nitrogen, giving cyclization and eliminating the chloride ion *via* an S_N2-like reaction (transition state A), resulting in the formation of aziridine **6**. In the case of *erythro*-**5**, steric repulsion by the axial methyl group stopped the attack of nitrogen (transition state B). In contrast, the 1,2-elimination reaction occurred only for *erythro*-**5** to give (*E*)-dehydroamino acid **7**‖ as the sole product. The results are explainable by Newman projections. The dissociated caesium ion acts as a base allowing the elimination of the chloride ion and *anti*periplanar proton, afforded 1,2-eliminated product **7** from *erythro*-**5** (transition state D), while *threo*-**5** cannot adopt a conformation able to 1,2-eliminate due to steric repulsion between the methyl, *N*-trityl and methoxycarbonyl groups, blocking reaction (transition state C).

In summary, we have shown here that (*S*)-*N*-tritylaziridine-2-carboxylate esters are quantitatively synthesized *via* the weak base-catalyzed cyclization of (*S*)-*N*-trityl-β-haloamino acid esters under mild conditions. By changing slightly the reaction conditions, 1,2-elimination takes place and affords *N*-trityl-dehydroalanine esters in good yield. Syntheses of (*S*)-amino acid derivatives by ring opening of the aziridine esters without racemization are currently underway.

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Notes and references

† BCA was enzymatically synthesized in high chemical (> 90%) and optical (> 99.9% ee) yields from 3-chloropyruvate using alanine dehydrogenase from *Bacillus stearothermophilus* (Unitika, Kyoto, Japan) with regeneration of NADH by formate dehydrogenase (Boehringer Mannheim GmbH, Germany) as described previously (ref. 10). The BCA was converted to *N*-Tr-BCA esters by an esterification with $SOCl_2$ in an appropriate alcohol followed by *N*-tritylation with Tr-Cl–Et_3N in CH_2Cl_2.

‡ *Selected data* for **3**: δ_H(400 MHz, $CDCl_3$) 7.19–7.38 (m, 20H), 5.85 (br, 1H), 5.19 (s, 2H), 4.86 (dd, 1H, *J* 0.85, 1.7), 3.73 (d, 1H, *J* 0.85); δ_C(100 MHz, $CDCl_3$) 165.9, 144.5, 136.6, 135.6, 129.1, 128.5, 128.3, 128.0, 127.8, 126.8, 95.4, 71.2, 67.3; ν_{max}/cm^{-1} (NaCl) 3400, 3060, 3030, 1705, 1615, 1485, 1440, 1295, 1195, 1170, 745, 695; mp 164–166 °C.

§ *Selected data* for **2**: δ_H(400 MHz, $CDCl_3$) 7.47–7.49 (m, 6H), 7.31–7.39 (m, 6H), 7.18–7.25 (m, 8H), 5.21 (ABq, 2H, *J* 3.8, 18.6), 2.28 (dd, 1H, *J* 1.5, 2.5), 1.92 (dd, 1H, *J* 2.5, 6.2), 1.41 (dd, 1H, *J* 1.5, 6.2); δ_C(100 MHz, $CDCl_3$) 171.4, 143.6, 135.8, 129.3, 128.6, 128.4, 128.3, 127.7, 126.9, 74.4, 66.7, 31.8, 28.8; ν_{max}/cm^{-1} (NaCl) 3060, 3030, 1740, 1590, 1485, 1445, 1235, 1170, 1015, 745, 705, 695, 625; mp 115–116 °C; $[\alpha]_D^{20}$ −96.9 (*c* 1.0, $CHCl_3$); optical purity > 99.9% ee [determined by HPLC with Crownpak CR(-) (Daicel, Tokyo, Japan) after derivatization of **3** to (*S*)-alanine by hydrogenation with Pd/C].

¶ Typical reaction procedure: to a stirred suspension of $KHSO_3$ (2.5 mmol) in anhydrous MeCN (15 ml) was added *N*-Tr-BCA ester (0.5 mmol) and the mixture was refluxed for several hours. After cooling to room temperature, 5 ml of 5% $NaHCO_3$ was added to the mixture and the product was extracted with CH_2Cl_2 (15 ml × 2). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (silica gel) and afforded aziridines as crystals or an oil.

‖ The structure of aziridine **6** and dehydroamino acid **7** were confirmed by ^1H and ^{13}C NMR and IR in comparison with reported values (ref. 11).

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